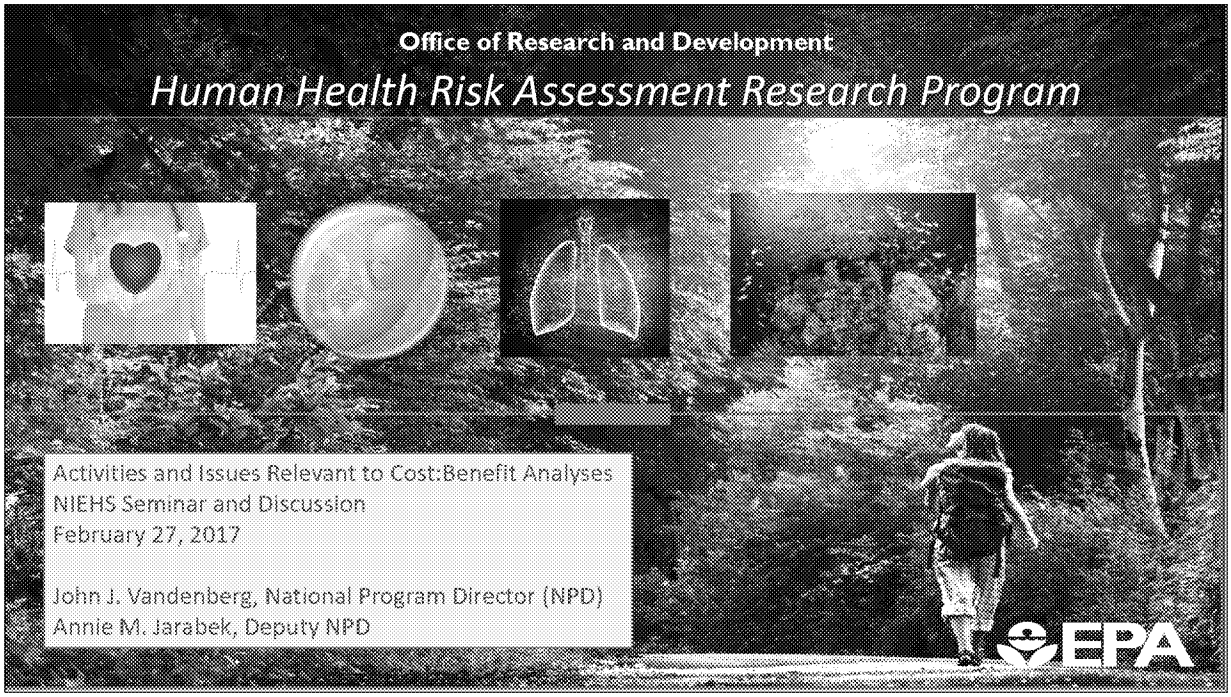
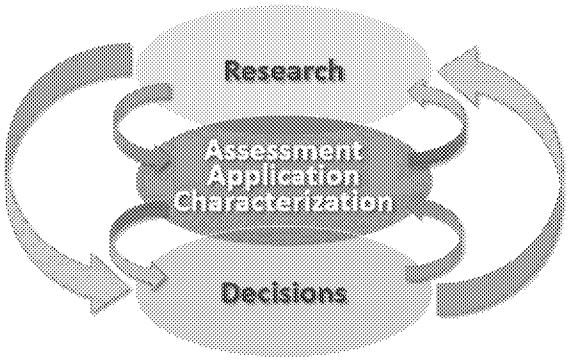

Office of Research and Development
Human Health Risk Assessment Research Program
Activities and Issues Relevant to Cost:Benefit Analyses
NIEHS Seminar and Discussion
February 27, 2017
John J. Vandenberg, National Program Director (NPD)
Annie M. Jarabek, Deputy NPD
EPA

Today's Topics

- Creating context: Assessment applications and emerging data
  - Role in research translation
  - Advancing public health protection and intervention
- Challenge: Establishing causality or correlation
  - Disease dimensions
  - Determining adaptive versus adverse
- Conceptual constructs and building bridges
  - Systems biology
  - Clinical signatures
  - Exposure-driven scenarios
- Currently planned projects: *Selections*

HHRA: Pivotal Role in ORD Portfolio



HHRA Vision: *Risk-based decisions by the EPA, State/local/tribal agencies and the public to protect public health and the environment are based on reliable, transparent and high-quality risk assessment methods, models, and data.*

HHRA Addresses all Agency Priorities and Mandates

HHRA

- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)

Broad Input to Support

- Agency Strategic Goals
- Children's Health, Environmental Justice, Climate and Nitrogen Roadmaps
- Sustainability

Risk Assessment Landscape

Type	Screening & Prioritization	Limited or Specific Scope	National Standard
Application	Rank chemicals of potential concern	Hazard ID or establish health benchmark to serve as guidance for actions such as SF site clean-up or TSCA use scenario	National-scale criterion to protect public health

Application Dimensions

- Regulatory requirements
- Evidence consensus
- Degree of Verification
- Data specificity
- Predictive Capacity

Computational Strategy: ***Mining / Abstraction*** ⟹ ***Directed Model Structures***

Applying Hazard ID and Risk Research to Inform Benefits Assessment

- **Assessing benefits requires characterizing the expected change in risk or outcome in a human population for a well-defined health outcome**
- **Necessary elements include:**
  - **Individual or human population level exposures to the stressor,**
  - **Identifying the most relevant human health outcomes (preferably those that have or could have an economic value assigned),**
  - **Exposure-response or dose-response relationship(s) that characterize the incremental change in risk or outcome for an incremental change in exposure or dose, and**
  - **An accounting for heterogeneity in either exposure or susceptibility**
- **"New" or "emerging" health outcomes or "endpoints" based on risk assessment research might address these elements either through epidemiology or via mechanistic models**
  - **Evaluation of the overall body of scientific evidence is critical first step towards ultimate valuation**
  - **Research on new approaches informs how prevention may improves public health and minimizes economic burden**

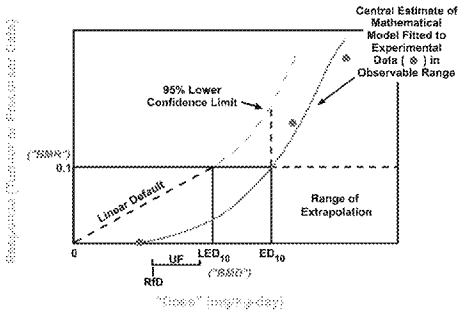
Example Dose-Response Analysis

$$RfD = \frac{POD\ [HEE]}{UF}$$

Where:

POD [HEE] = The point of departure or level of concern that is dosimetrically-adjusted to a human equivalent exposure [HEE]. Typically defined by a No-Observed-Adverse-Effect Level (NOAEL) / Lowest-Observed-Adverse-Effect Level (LOAEL) approach or benchmark dose (BMD) model.

UF = Uncertainty factor(s) applied to account for the extrapolation required from the characteristics of the experimental regimen to the assumed human scenario.



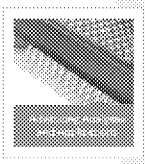
Assessing Associations

Challenge: Is the marker truly an intervening variable or merely a confounding factor?

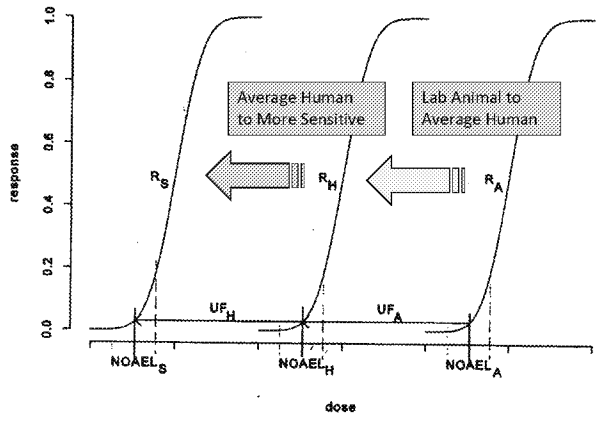
- **Conventional epidemiological techniques for screening disease and handling multiple variables**
- **Determine the extent marker reflects recent or past and peak versus integrated exposure, cumulative or non-cumulative effects**
- **Hill criteria for the association:**
  - **Temporal, coherence, dose-response, consistency, strength, specificity**
- **Emergence of process or mechanistic modeling to enhance empirical**
- **Seasoned judgment of the best available information in the face of lack of mechanistic data**

Project 7 (HHRA 4.21): Advancing Hazard Characterization and Dose-response Methods

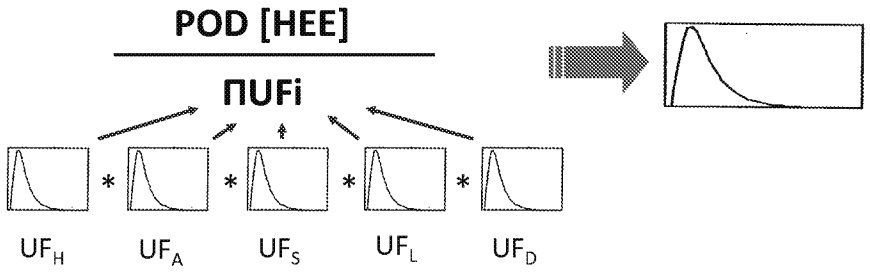
- **Task 7.3 (HHRA 4.213): Advancing Methods for Benefits and Uncertainty Analyses** (TLs Todd Blessinger / Tom Bateson, NCEA W)
- **Collaboration with Office of Policy (OP):** Chris Dockins, Charles Griffiths, Dan Axelrad, Al McGartland
  - Recent work examines methods for adapting/applying exposure-response functions from epidemiology studies to inform benefits analyses
  - Planned as appendix to the IRIS formaldehyde assessment



Typical Default Extrapolations Applied to Address Uncertainty



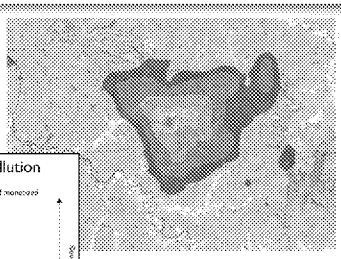
Probabilistic Reference Value Derivation

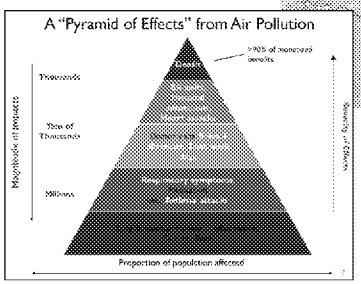


Hasselblad, V. and Jarabek, A.M. (1996) Chapter 8: Dose-Response Analysis of Toxic Chemicals. In: Bayesian Biostatistics, (Eds.) D.A. Berry and D.K. Stangl, Marcel Dekker, New York, pp. 235–259.
Baird, J.S., Slob, W. and Jarabek, A.M. (2001) Probabilistic Noncancer Risk Estimates. *Comm. Toxicol.* **7,** 541–574.
Baird, S.J. et al. (1996) Noncancer risk assessment: A probabilistic alternative to Current practice. *Human Ecol. Risk Assess.* **2(1),** 79-102.
Swartout, J.C. et al. (1998) A probabilistic framework for the Reference Dose (Probabilistic RfD). *Risk Anal.* **18(3),** 271-282.

Emerging Approaches: Multi-scale Modeling

- **Flexibility required to**
  - **Characterize different exposure scenarios**
    - **Acute**
    - **Episodic**
    - **Chronic**
  - **Address different scales**
    - **Geographical**
    - **Temporal**
    - **Biological**
  - **Describe disease dimensions (e.g., early or late event) and key events**
  - **Develop probabilistic approaches**





The motivation and need is really one of creating context and building capacity for multi-scale modeling. Characterization of real-world exposure scenarios requires flexibility to address complexity: i.e., for various exposure durations & across different scales. Ultimately, to properly characterize the potential effects of different exposures, either for a community or for an individual, we need to understand and describe the disease pathogenesis. This will help develop probabilistic approaches based on key events leading to disease which will both inform intervention and support benefit:cost analyses.

"Place-based" Dose Translation and Data Integration

- **Data from diverse sources and approaches require dose translation to facilitate interpretation**
  - **Community and ecosystem sensors**
  - **Human studies (clinical, epidemiological)**
  - **Laboratory animal (*in vitro, ex vivo, in vivo*) → IVIVE**
  - **Biomonitoring**
  - **Clinical chemistry**
  - **Virtual tissues**
  - **HTS / HC**

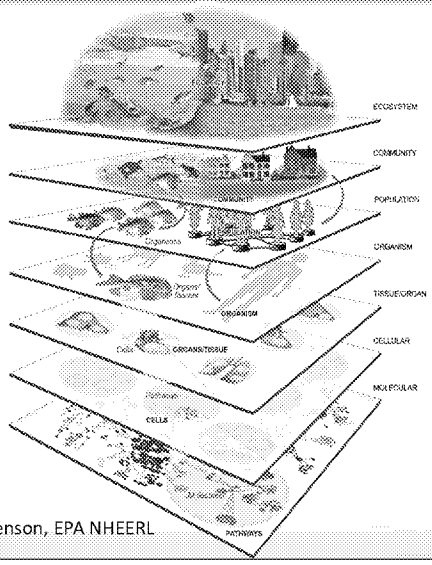


Figure courtesy of Bill Benson, EPA NHEERL

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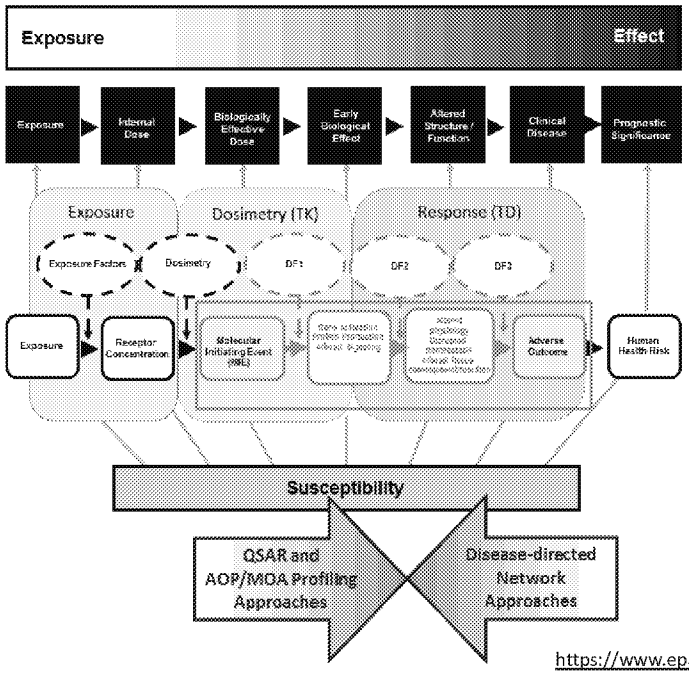
To apply emerging data in risk assessment, we need to create context for dose translation and data integration across different experimental platforms, and to build bridges to both the clinical arena (e.g., signatures or profiles used to predict pathogenesis for specific diseases such as renal failure) as well as emerging community measurements (e.g., Citizen science and sensor data).



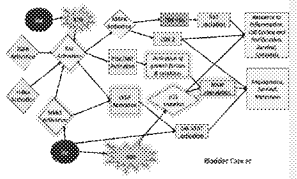
Evidence Integration and Evolution of Risk Assessment

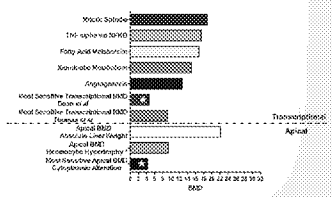
- Convergence of conceptual frameworks
  - Biomarker
  - MOA
  - AOP
- Integration
  - Levels of organization
  - Key events across species
- Interoperable model components

https://www.epa.gov/research/strategic-research-action-plans-2016-2019

Project 8 (*HHRA 4.22*) – Applying Emerging Science to Inform Risk Screening and Assessment

- ***Building confidence: Characterization to Advance Applications***
  - an iterative and integrated approach to foster understanding and trust of new techniques
- **Task 8.1 (HHRA 4.21): Disease-based integration of new data types** (TL Ila Cote, NCEA IO)
  - Inorganic arsenic case study: Exploration of disease-based AOP
- **Task 8.2 (HHRA 4.22): Characterization and Quantitative Application of High-throughput Screening (HTS) and Other Data-mining Derivations** (TL Scott Wesselkamper, NCEA CIN)
  - Dean JL et al. (2017). Application of Gene Set Enrichment Analysis for Identification of Chemically-induced, Biologically Relevant Transcriptomic Networks and Potential Utilization in Human Health Risk Assessment. *Toxicol. Sci.* [Epub ahead of print] https://academic.oup.com/toxsci/article-lookup/doi/10.1093/toxsci/kfx021





Advantages of Mechanistic Approaches

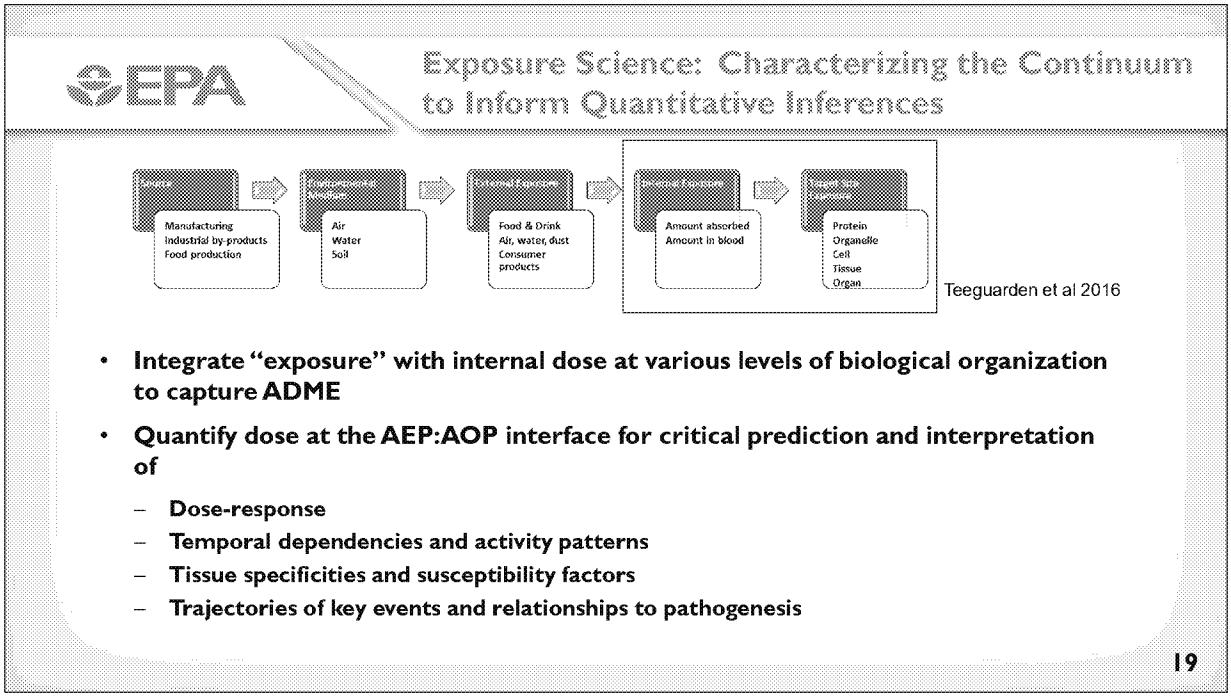
- Emphasize full characterization: exposure-dose-response
- Consider endpoint domain
- Aid understanding of disease dimension
- Facilitate development and validation of biomarkers and key events
- Motivate more sophisticated quantitative models
  - Semi-empirical
  - Biologically-based dose-response
- Allow iterative refinement as knowledge increases

Considerations for Extending the Range of Observation and Establishing Prognostic Significance

- Validation
  - Construct: *corresponds to theory*
  - Content: *incorporates domain*
  - Criterion: *correlates with external measure*
- Causal linkage or correlation
  - Mode versus myriad of mechanisms
  - Designation of adversity — biological & statistical basis
  - Identify potential susceptible subpopulations
- Confidence in description / calculation
  - Parameter estimation / identifiability
  - Limits of resolution in data
  - Criteria for integration of diverse data
- Uncertainty analysis
  - Role of inadequate understanding
  - Data gaps
  - Vagueness in process or parameter definition
  - Measurement error
  - Sampling error
- Variability

Considerations for Regulatory Acceptance: Extrapolation to Human Equivalence

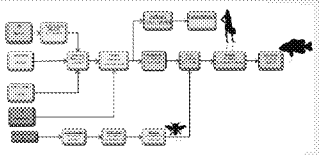
- **Interspecies extrapolation**
  - **Fidelity to appropriate system(s), behavior(s) and mechanism(s)**
  - **Validation**
- **Mechanistic versus default or categorical derivation**
  - **"Data derived" a function of domain (chemical, level of organization, effect)**
- **Aim @ accuracy**
  - **Predictive rather than presumably protective**
  - **Confidence versus uncertainty: Value of information**



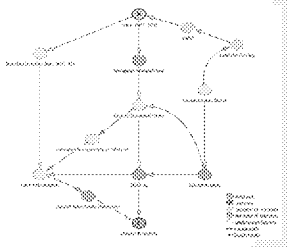
Environ Sci Technol. 2016 May 3;50(9):4579-86. doi: 10.1021/acs.est.5b05311. Epub 2016 Feb 10.
Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework.
Teeguarden JG1,2, Tan YM3, Edwards SW4, Leonard JA5, Anderson KA2, Corley RA1,2, Kile ML6, Simonich SM2, Stone D2, Tanguay RL2, Waters KM1,2,Harper SL2,7, Williams DE2.

Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- **Task 6.1 (HHRA 3.231) Approaches to cross-species data integration (collaboration with NHEERL)**
  - SOT 2017 RASS Best Abstract Award – (Abstract # / Poster #: 2827/P229) on Wednesday March 15: David Hines et al. *Cross-species integration of human health and ecological endpoints using the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to advance risk assessment*

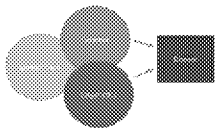


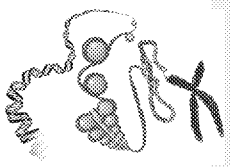
- **Task 6.2 (HHRA 3.232) Incorporating multiple stressors** (TL Glenn Rice, NCEA CIN)
  - Completed early (FY16): Workshop report: Greenspace (GS) exposure and health effects occurrence from a CRA perspective. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=314417
  - FY16 Q4: Brewer LE, Wright JM, Rice G, Neas L, Teuschler L. (Accepted – galley proof stage). Causal inference in cumulative risk assessment: The roles of directed acyclic graphs. *Environ. Int.*



Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

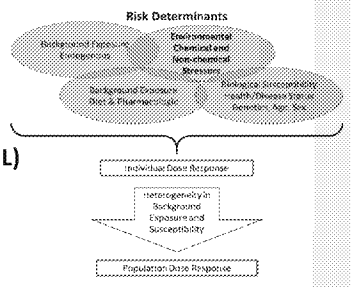
- **Task 6.3 (HHRA 3.233): Applying Genetic and Epigenetic Data to Inform Susceptibility** (TL Sue Euling, NCEA W)
  - **Subtask: Applying Epigenetics Data to Cumulative Risk**
    - **Human Study: Nonchemical Stressors, Epigenetic Changes, Susceptibility to Air Pollution Exposure, and Cardiovascular Disease** ***(HHRA, ACE, and SHC Collaboration with NHEERL on Duke CATHGEN project)***
    - **Epigenetics and Cumulative Risk Assessment Workshop Report**
  - **Subtask: Applying Polymorphism and Mechanistic Data to Inform Genetic Susceptibility**
    - **Approach and Case Study: Use AOP Framework and Select Relevant and Data Rich AOP for Case Study**





Project 6 (*HHRA 3.23*): Cumulative Risk Assessment Methods and Applications

- **Task 6.4 (HHRA 3.234): Apportioning Multimedia Exposure and Risk Across Human and Ecological Receptors** (TL Jennifer Richmond-Bryant, NCEA RTP)
- **Focus of tasks: multiple stressor, multimedia exposures**
  - Advances in modeling exposure apportionment
    - Modeling dermal and inhalation exposures to phthalates
    - Apportioning chemical stressors for the most affected portions of the populations of human and ecological receptors **(Collaboration with NERL)**
    - Chemical and physical properties of multiple stressors
  - Application of exposure apportionment methods
    - Breastfeeding as a route of exposure for environmental chemicals
    - Cumulative exposures, social determinants, and health **(Collaboration with R3)**
    - Pharmacokinetic modeling of infant body burden from bioaccumulative compounds in mother's milk
    - Residential exposure to pesticide active ingredients and birth defects **(Collaboration with NHEERL)**



Informing Benefits of Prevention

- Probabilistic and mechanistic approaches address current scientific areas of emphasis
  - Bridge to systems biology
  - Link to clinical signatures and intervention evaluation
- Provide enhanced understanding of pathogenesis to motivate new outcome measures
  - Appreciation of disease dimension
  - Identification of biomarkers and key events
- Converts uncertainty descriptions to characterization of confidence
- Extend capability of computational modeling and provides platform for future applications
  - Formal statistical bounding
  - Multi-media, multi-chemical, multi-scale, multi-species → cumulative
  - Amenable to exposure and economic analyses

Acknowledgments

- Kris Thayer, EPA ORD
- Bryan Hubbell, EPA ORD
- Barbara Soares, NIEHS
- Dan Axelrad, EPA ORD
- Jason Sacks, EPA ORD
- Tom Bateson, EPA ORD

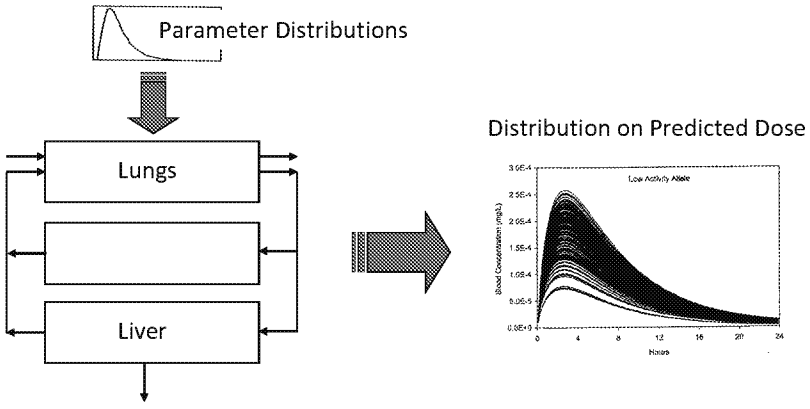
Extra Slides

Background

Uncertainty Analysis in Risk Assessment

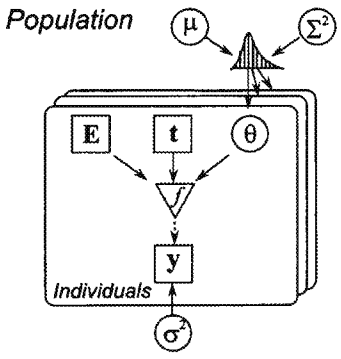
- Noncancer approaches employ uncertainty factors
  - Not mechanistically motivated
  - Not independent but so applied
  - "Data-derived" new area of emphasis but strategies to date remain empirical
    - Stratified by category: chemical class or endpoint
    - Do not integrate multiple effects or levels of organization
  - Oral route and Outdated
- PBPK characterizations
  - Markhov Chain Monte Carlo (MCMC) or sensitivity analyses
  - Essentially restricted to parameter bounding with little impact on UF or on estimate outcome
  - 2-D may address uncertainty versus variability
- Cancer approaches
  - Same as above

PRA applications in PBPK modeling



Gentry, P.R. et al. (2002) An approach to the quantitative consideration of genetic polymorphisms data in chemical risk assessment: Examples with warfarin and parathion. *Toxicol. Sci.* **70,** 120-139.

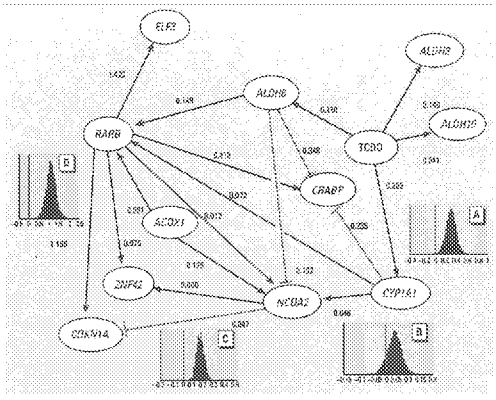
PRA Population Modeling



- Introduced for drug development and efficacy evaluation
- Objective is to extract from individual units (e.g., subject, family group) a quantitative description of kinetics of a compound within a large population
- Exposure (E), time (t) and individual parameters (θ) condition the observation (data, y). Relationships between E, t, θ, and y) described by model, f.
- Population means and variance (μ and $\sum^2$) describe shape of distribution.
- Measurement errors and intraindividual variability are lumped in common variance term (σ^2).

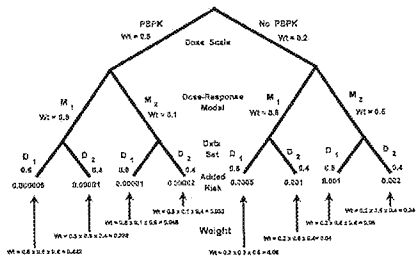
Bois, F.Y. (2001) Applications of population approaches to toxicology. *Toxicol. Lett.* **120,** 385-394.

Genetic regulatory networks

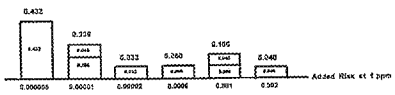


Toyoshiba, H. et al. (2004) Gene interaction network suggests dioxin induces a significant linkage between aryl hydrocarbon receptor and retinoic acid receptor Beta. *Environ. Health Perspect.* **112(12),** 1217-1224.

Weighted Probability Tree



Alternative analyses weighted by plausibility



Resultant distribution for risk estimate

Sielken, R.L. (1995) How to use both human and animal data in quantitative Risk assessment. In: The Role of Epidemiology in Regulatory Risk Assessment, J.D. Graham, Ed. Elsevier Sciences.

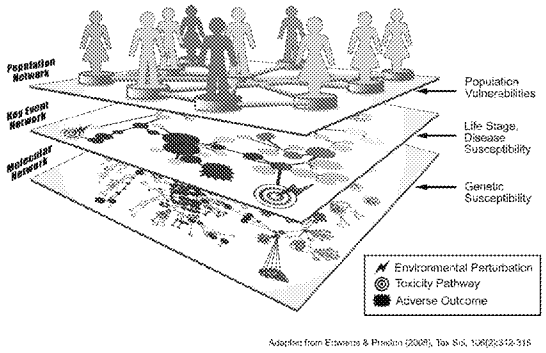
- Task 4.221: Disease-based integration of new data types **(TL Ila Cote)**

— MOAs can be used improve almost every aspect of risk assessment, and they can be built most efficiently and robustly using new methods

— MOA aid understanding of: biomarkers of exposure and effect, susceptible subpops/lifestages, mixtures interactions, hazard ID for data poorer chemicals, and dose-response (potentially)

— In the inorganic arsenic (iAs) case study, we have used molecular and computational MOA to generate 10 human-based AOPs for cancer (e.g. bladder, lung) and noncancer diseases (atherosclerosis, diabetes).

— These can be used to better understand iAs and other chemical that cause these diseases



Adapted from Edwards & Preston (2008), Tox Sci, 106(2):312-315

Task 4.221: Disease-based integration of new data types

- Basic AOP network (gray) provided by NIH BioSystems
- Yellow diamonds are iAs-specific gene transcription changes
- Yellow squares are traditional iAs exposure outcomes driven by the identified gene transcription changes
- Green highlights represent events further modified by tobacco smoke
- We understand the dose-response relationships for several genes